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ARTICLE

Population pharmacokinetic analysis of the P2X3-receptor antagonist gefapixant

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Abstract

Gefapixant, a P2X3-receptor antagonist, demonstrated objective and subjective efficacy in individuals with refractory or unexplained chronic cough. We report a population pharmacokinetic (PopPK) analysis that characterizes gefapixant pharmacokinetics (PKs), quantifies between- and within-participant variability, and evaluates the impact of intrinsic and extrinsic factors on gefapixant exposure. The PopPK model was initially developed using PK data from six phase I studies. Stepwise covariate method was utilized to identify covariates impacting PK parameters; the model was re-estimated and covariate effects were re-assessed after integrating PK data from three phase II and III studies. Simulations were conducted to evaluate the magnitude of covariate effects on gefapixant exposure. Of 1677 participants included in this data set, 1618 had evaluable PK records. Age, body weight, and sex had statistically significant, but not clinically relevant, effects on exposure. Degree of renal impairment (RI) had statistically significant and clinically relevant effects on exposure; exposure was 17% to 89% higher in those with versus without RI. Simulation results indicated that gefapixant 45 mg administered once daily to patients with severe RI has similar exposure to gefapixant 45 mg administered twice daily to patients with normal renal function. There were no significant effects of proton pump inhibitors or food. Of evaluated intrinsic and extrinsic factors, only RI had a clinically relevant effect on gefapixant exposure. Patients with mild or moderate RI do not require dosage adjustments; however, for patients with severe RI who are not on dialysis, gefapixant 45 mg once daily is recommended.

Akshita Chawla and Anna Largajolli contributed equally to this work.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Gefapixant, a P2X3-receptor antagonist, is approved in Japan and Switzerland for treatment of refractory chronic cough (RCC) or unexplained chronic cough (UCC); pharmacokinetic (PK) characteristics of gefapixant in healthy volunteers were previously published.

WHAT QUESTION DID THIS STUDY ADDRESS?

A population PK (PopPK) model was developed to further characterize gefapixant PKs and assess the impact of intrinsic and extrinsic factors on PKs in healthy participants and participants with RCC or UCC. Additionally, this analysis provides a framework for dosage recommendations in the target population.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This work confirms that most intrinsic and extrinsic factors, except renal function, have minimal impact on gefapixant exposure and that gefapixant 45 mg once daily (rather than twice daily) is optimal for patients with severe renal impairment (RI) who are not on dialysis.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

PopPK models were used to inform gefapixant dosage recommendations in individuals with RCC or UCC, including those with severe RI who were not included in the phase II/III trials.

INTRODUCTION

Chronic cough, characterized by frequent, burdensome cough lasting greater than 8 weeks, affects 4% to 18% of adults.[1–4] Until recently, there were no approved treatments indicated for chronic cough; thus, many patients have received medications targeting common comorbidities of chronic cough that are often ineffective, leading to a large unmet need for this population.[5,6] Gefapixant is a first-in-class, selective P2X3-receptor antagonist approved in Japan and Switzerland for refractory chronic cough (RCC; persistent cough despite extensive investigation and appropriate treatment of comorbid conditions per published guidelines) and unexplained chronic cough (UCC; persistent cough with no identifiable cause despite thorough workup).[7–9] P2X3 receptors, which are gated by adenosine triphosphate (ATP), are expressed on sensory C-fibers of the vagus nerve in the airways; P2X3-receptor binding of extracellular ATP triggers action potentials that ultimately trigger a cough reflex.[10–13] Although the precise mechanisms underlying RCC and UCC are not elucidated, extracellular ATP signaling in response to tissue damage and inflammation has been proposed as a driver of chronic cough.[14–17] The therapeutic benefit of P2X3-receptor antagonism has most recently been supported by two large phase III studies, in which gefapixant 45 mg twice daily (b.i.d.) improved 24-h cough frequency after 12 (COUGH-1, NCT03449134) and 24 (COUGH-2, NCT03449147) weeks of treatment, with significant improvements in cough-specific quality of life after 24 and 52 weeks of treatment.[18,19]

Pharmacokinetics (PKs) of gefapixant have been evaluated in clinical studies. Oral dosages of gefapixant ranging from 7.5 to 1800 mg b.i.d. have been evaluated in healthy participants in phase I studies. In phase II studies of participants with RCC or UCC, dosages up to 600 mg b.i.d. for 4 weeks and up to 50 mg b.i.d. for 12 weeks were evaluated, whereas the phase III studies evaluated 15- and 45-mg b.i.d. dosages for up to 1 year.[19–21] Previous PK analyses have demonstrated that gefapixant is rapidly absorbed, with the time to reach maximum observed concentration ranging from 1 to 4 h, an elimination half-life of 6 to 10 h, and dose-proportional PKs within the clinical dose range.[22] Gefapixant is primarily eliminated via renal excretion.[23]

This analysis describes the development of a population PK (PopPK) model for gefapixant using PK concentrations from healthy participants and participants with RCC or UCC across several clinical phase I, II, and III studies. Overall goals for this analysis are to (1) characterize the PK profile of gefapixant in healthy participants and participants with RCC or UCC, (2) quantify the between- and within-participant variability of gefapixant PKs, and (3) evaluate and quantify intrinsic (e.g., body weight, age, race, and renal impairment [RI]) and extrinsic (e.g., food, proton pump inhibitor [PPI]) effects on gefapixant PKs.

METHODS

Study objectives and design

The modeling analysis data set included intensively sampled PK data from six phase I studies and sparse PK data from one phase IIb and two phase III studies (Table S1). Included studies investigated gefapixant formulations closely related to the marketed formulation (Tables S1 and S2). These studies included doses in the range where gefapixant PKs demonstrated dose-proportional increases. All studies were conducted in compliance with the ethical principles set forth in the Declaration of Helsinki and according to guidelines resulting from the International Conference on Harmonization and Good Clinical Practice. All participants provided written informed consent.

Phase I studies

The six phase I studies (Table S1) supported development of the structural PK model; allowed for characterization of food and PPI effects; and provided information on the effect of RI on gefapixant PKs in participants with mild, moderate, or severe RI. Data from individuals with end-stage renal disease (ESRD) and from studies using gefapixant formulations preceding the F02 formulation (e.g., F01) were excluded.

Phase II and III studies in RCC and UCC

The phase IIb study was a 12-week, randomized, double-blind, placebo-controlled study in adults with RCC or UCC recruited throughout the United Kingdom and United States.[21] Two phase III, global, randomized, double-blind, placebo-controlled studies with main study periods lasting 12 (COUGH-1) and 24 (COUGH-2) weeks were also included.[24] The phase III studies had blinded extension periods lasting through 52 weeks; PK data analyzed here were obtained during the 12- and 24-week periods, with a sensitivity analysis performed to evaluate the impact of additional PK data during the 52-week extension. Data from the phase IIb and phase III studies enabled a thorough assessment of covariate effects on gefapixant PKs.

Gefapixant formulations

Several formulations of gefapixant have been evaluated in clinical studies; this analysis includes data from the F02, F04, and F04A formulations. F02 (developed via wet granulation and used in several phase I studies and the phase IIb RCC/UCC study) includes an acidulant (citric acid) and is a film-coated, immediate-release tablet in 7.5-, 20-, and 50-mg strengths. F04 (used in two phase I studies) contains gefapixant citrate as an active ingredient with a 20A film coating. F04A (evaluated in COUGH-1 and COUGH-2) also contains gefapixant citrate as an active ingredient, with a 03K film coating.

Analysis

Modeling strategy

Model development steps are illustrated in Figure 1. A structural model was initially developed using phase I data (defined as the base model). The impact of extrinsic factors (e.g., food intake and PPI use) on absorption rate constant (K_a) and relative bioavailability was investigated relative to the F02 formulation as part of base model development. Previous studies demonstrated a lack of food and PPI effects on the F04 formulation[25]; thus, such effects were not tested for F04. As gefapixant is primarily a renally cleared drug, the estimated glomerular filtration rate (eGFR) was also tested as a covariate as part of base model development. The final base model was the starting point for the stepwise covariate model (SCM) development and was used to test relevant covariate relationships with apparent clearance (CL/F) and apparent central volume of distribution (Vc/F). The list of candidate covariates to be tested in the SCM was guided by exploratory covariate evaluation and scientific plausibility (Figure S1). Effects of continuous covariates, such as age or weight, on model parameters were tested as a power function centered on the median covariate as follows:

$$P_i = P_{TV}\left(\frac{cov_i}{\widetilde{cov}}\right)^{\theta} \bullet e^{\eta_i}$$

Effects of categorical covariates, such as sex, on model parameters were tested as follows:

$$P_i = P_{TV}\left(1 + \theta_{cov,c} \bullet I_{cov,c,i}\right) \bullet e^{\eta_i},$$

in which $\theta_{cov,c}$ is the fractional change in P per category of covariate cov, and $I_{cov,c,i}$ is an indicator variable, having a value of 0 for the most common category and a value of 1 corresponding to each of the other existing categories.

Stepwise forward selection was based on a statistical significance level (α) of 0.01 (requiring an objective function value [OFV] reduction of 6.63 for 1 degree of freedom [df]); stepwise backward elimination was based on α of 0.001 (requiring an OFV increase of 10.83 for 1 df). Other acceptance criteria included a decrease in relevant

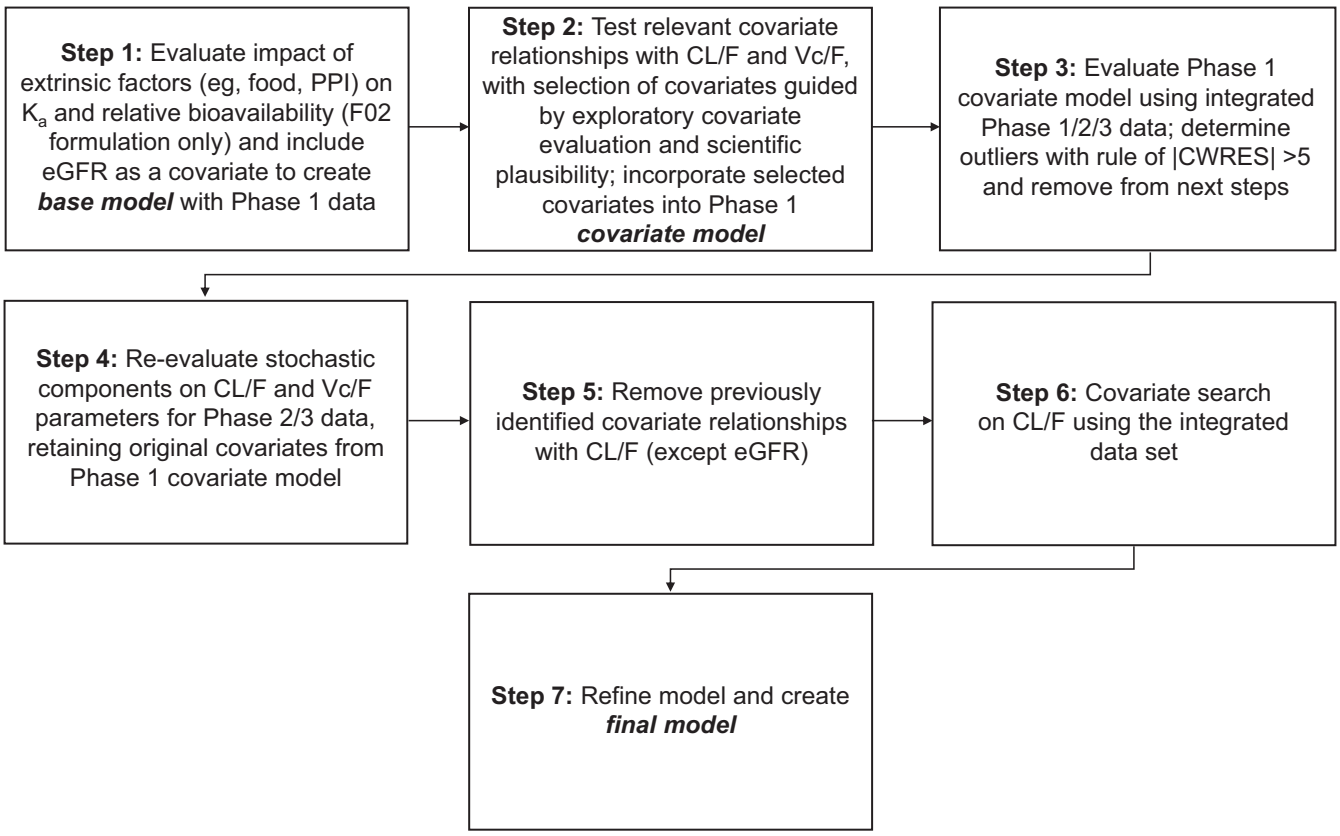

FIGURE 1 Schematic diagram of PopPK model development. CL/F, apparent clearance; |CWRES|, absolute value of the conditional weighted residuals; eGFR, estimated glomerular filtration rate; K_a, absorption rate constant; PK, pharmacokinetic; PopPK, population PK; PPI, proton pump inhibitor; Vc/F, apparent central volume of distribution.

variance components, improvement in precision of parameter estimates, improvement in diagnostic plots, and model stability. The clinical relevance of any relationship was also considered. The covariate model developed using phase I data will be referred to as the phase I covariate model.

The phase I covariate model was re-estimated and re-assessed after integrating sparse PK data from phase II and III studies. During the re-estimation process, an outlier exclusion on the newly added data from phase II and III studies was deemed necessary as the estimate of apparent peripheral volume (Vp/F) was implausibly high. An evaluation step (MAXEVAL = 0) was conducted, keeping the population parameters fixed to estimates of the phase I covariate model. Outliers were determined using conditional weighted residuals (CWRES), with the rule of |CWRES| greater than 5. After the exclusion of these outliers, the re-estimation step was completed.

At this stage, stochastic components (interindividual variability [IIV] on PK parameters) were re-evaluated. The optimized stochastic model was used for further model development. Because the sparse phase II/III data were unlikely to inform covariate effects on K_a, Vc/F, or Vp/F estimations, the covariates already identified in the phase I model were retained, and these covariate effects were re-estimated using the integrated data set. The previously identified covariate relationship with CL/F (i.e., body weight) was removed from the model (apart from the covariates included in the base model), and a second round of covariate assessment was done on CL/F using the integrated data set. This model was refined to create the final model. Model diagnostics and goodness-of-fit plots were generated to assess model performance and robustness.

Simulations

Simulations estimated exposure in the target population (i.e., RCC and UCC) and quantified the magnitude of covariate effects in RCC and UCC. Furthermore, exposure in participants with various degrees of RI was estimated for both b.i.d. and once-daily (q.d.) regimens. The first simulation estimated exposure in the target population after chronic administration of gefapixant 45 mg b.i.d. In this simulation, 1366 participants from the active cohorts in COUGH-1 and COUGH-2 were sampled with replacement. The second simulation evaluated the magnitude of covariate effects on gefapixant PKs in the phase II and III participants, where 600 participants per covariate category

(i.e., age, sex, body weight, and RI) were sampled. The third simulation evaluated exposure in participants with RI. As the phase II and III studies did not enroll sufficient participants with moderate RI and any participants with severe RI, phase II and III demographic data were augmented with the phase I RI study and a virtual population database, which was a pooled Merck (Rahway, NJ, USA) database containing demographic information for participants with RI from different programs across therapeutic areas, including antibacterial, antiviral, neuroscience, cardiovascular, and metabolic disease and oncology ($N=2611$). The simulation assumed that demographic distribution in the virtual database was the same as that of the RCC/UCC population with RI by restricting the sex distribution and body weight range in the virtual population data set to match that of the participants with mild and moderate RI in the RCC/UCC population. From this augmented data set, 600 participants were sampled for each renal function category.

In all simulations, PK parameters (e.g., CL/F, Vc/F, and K_a) were generated using the final model by incorporating parameter uncertainty (only on fixed effects) and by accounting for IIV for each sampled participant. Area under the concentration curve versus time at steady-state ($AUC_{ss,0-12}$) and maximum concentration (C_{max}) were calculated, assuming that each participant received gefapixant 45 mg b.i.d. (in the phase II/III study population) or gefapixant 45 mg b.i.d. or q.d. (in populations stratified by RI categories). Geometric means and percentages of coefficient of variation were calculated for AUC and C_{max}. In addition, for RI simulations, geometric mean ratios (relative to normal renal function category) were calculated for each exposure metric. The process for each simulation was repeated 200 times.

RESULTS

Of 1677 participants included (healthy volunteers, $n=122$; RCC or UCC, $n=1555$), 1661 had at least one PK record and 16 had only dosing records, without any PK records (healthy volunteers, $n=1$; RCC or UCC, $n=15$). Across participants, 12,663 plasma concentrations were available; however, samples were excluded for various reasons, including inconsistent timing of dosing administrations before PK sampling, receipt of an extra dose within 3 days before PK sampling, measurable gefapixant concentrations before the first dose, and missing times of dosing (Figure 2). After exclusion, the final data set included 1618 participants with evaluable PK data (healthy volunteers, $n=121$; RCC or UCC, $n=1497$), including 8886 measurable gefapixant concentrations (number of participants included by study can be found in Table S2). Descriptive statistics of continuous and categorical covariates included in the PopPK data set stratified by populations are summarized in Table S3. Correlations among continuous covariates are presented in Figure S2.

Concentration-time profiles

The gefapixant dose-normalized concentration-time profiles for phase I studies (Figure 3a) demonstrate a biphasic nature of gefapixant elimination, suggesting a two-compartment PK model is needed to fit the data. Dose-normalized concentrations as a function of time after previous dosing for participants with RCC or UCC by study are presented in Figure 3b and are consistent with dose-proportional PKs.

Model development

The base model was developed using phase I data. As part of model development, the impact of extrinsic factors (i.e., food intake and PPI use) was investigated only for the F02 formulation on absorption parameters (absorption lag time and K_a) and bioavailability. All combinations were tested and retained in a stepwise manner until no further improvement in the model fit was supported by data. Fed status on K_a for only the F02 formulation was found

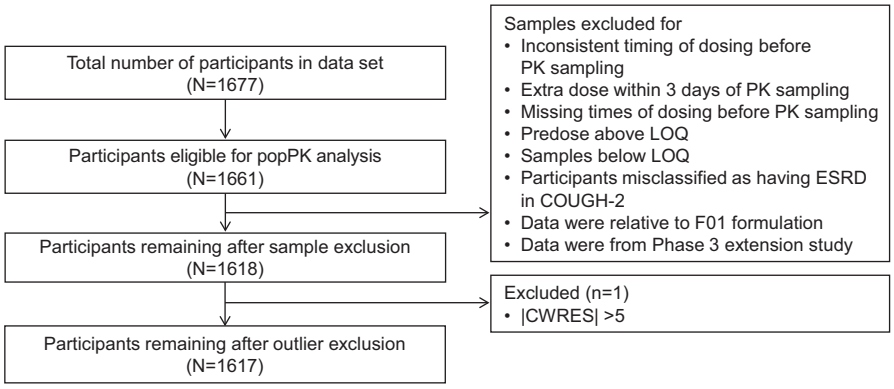

FIGURE 2 Data disposition for gefapixant PopPK analysis. |CWRES|, absolute value of the conditional weighted residuals; ESRD, end-stage renal disease; LOQ, lower limit of quantification; PK, pharmacokinetic; PopPK, population PK.

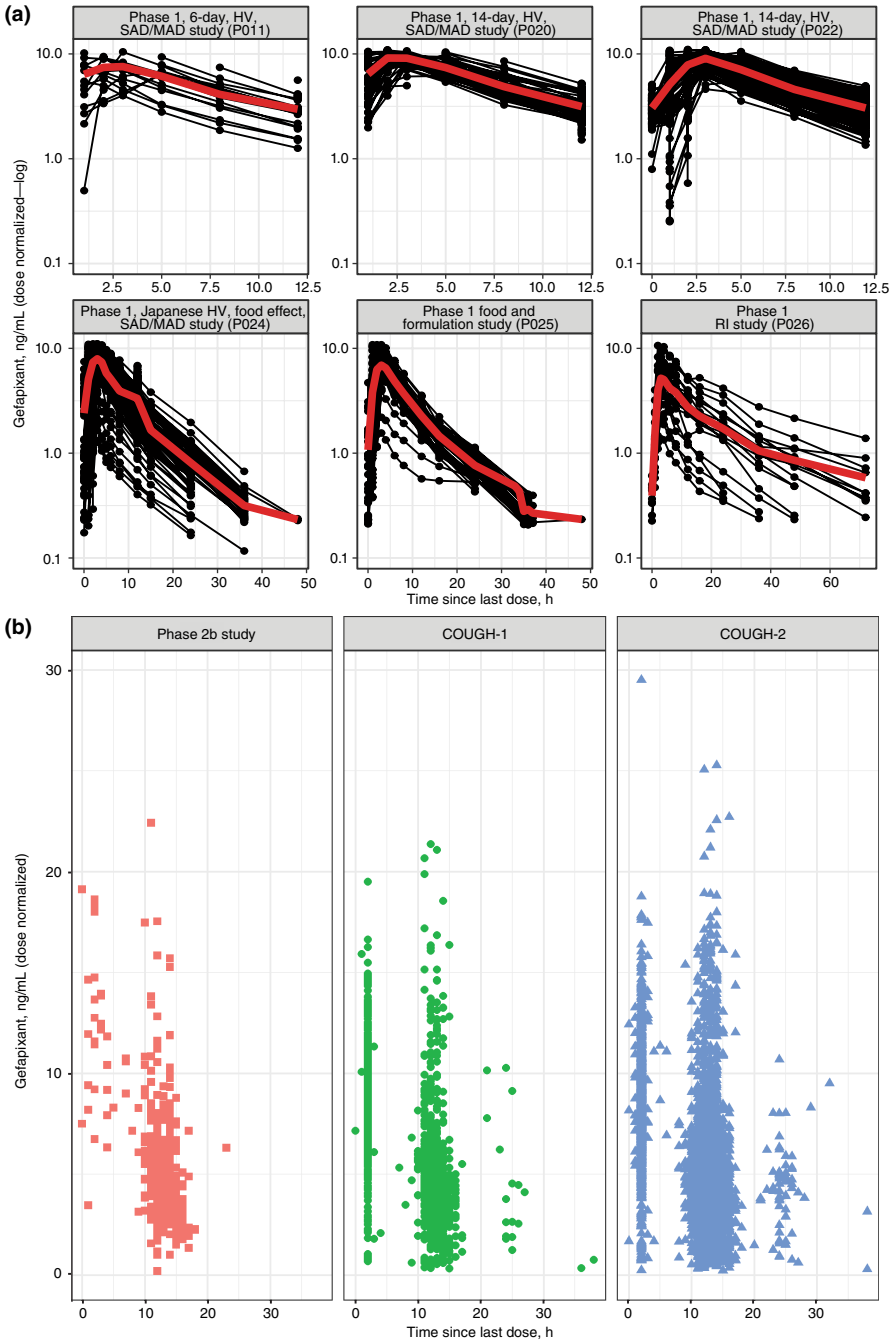

FIGURE 3 Gefapixant plasma concentration-time plots from (a) phase I studies (solid red line indicates the mean concentration-time profile) and (b) phase II and III studies in individuals with RCC or UCC. HV, healthy volunteer; MAD, multiple ascending dose; RCC, refractory chronic cough; RI, renal impairment; SAD, single ascending dose; UCC, unexplained chronic cough.

significant and was retained in the model. Subsequent testing of food and PPI use in the model did not identify other relations eligible for inclusion, either because of a nonsignificant drop in the OFV or poor parameter estimation (high relative standard error [RSE]). At this stage, eGFR was added as a covariate on CL/F as part of the base model. This base model was used to conduct the SCM to investigate the impact of age, sex, race, ethnicity, and baseline body weight on CL/F and Vc/F (body mass index was not evaluated because of its high correlation with body weight). Table S4 presents significant covariates identified during forward-selection and retained during backward-elimination processes. After forward-inclusion and backward-elimination steps, body weight on CL/F and body weight, age, and sex on Vc/F were retained; this model is referred to as the phase I covariate model.

The phase I covariate model was subsequently re-estimated and re-assessed using the integrated phase I through III data sets. At this stage, outliers were identified and excluded from further model development (Figure 2). Stochastic components were re-assessed using the integrated phase I through III data sets. Estimating IIV on only CL/F resulted in the biggest drop in the OFV; however, because of the correlation between CL/F and Vc/F, IIV terms on both CL/F and Vc/F were retained. In the final model, IIV on K_a was estimated from phase I data only, whereas IIV

on CL/F and Vc/F was estimated using all data. To allow an unbiased assessment of covariate effects based on the integrated phase I through III data sets, the previously identified covariate relationship with CL/F (i.e., body weight), but not eGFR (which was included in the base model), was removed from the model. As noted in the Methods, covariates on Vc/F or K_a already identified in the phase I covariate model were retained. This model was the starting model for final re-assessment of covariates on CL/F.

Age, baseline body weight, sex, race, and ethnicity were evaluated as potential covariates on CL/F. Table S5 presents results from forward-selection and backward-elimination processes, which identified body weight, age, sex, and race as significant covariates. The "multiple" race category, which constituted a small proportion (~5%) of the target population, was the only category with a non-negligible effect size (i.e., 0.19 vs. ~0.05 for other categories). Therefore, it was merged with the "other" race category, and race effect was ultimately removed from the final model. Parameter estimates, RSEs, and confidence intervals (CIs) of the final model obtained from bootstrap analysis of the final model are presented in Table 1. Most parameters were estimated with good precision. Excluding age on Vc/F (which had an RSE of 37%) and IIV on Vc/F (which had an RSE of 42%), RSEs were less than 25% for all parameters. Random-effect shrinkage was acceptable for the IIV on CL/F parameter (shrinkage 15%) but high for the IIV on Vc/F parameter (shrinkage 52%); epsilon shrinkage was acceptable (7%). High shrinkage suggests there are challenges in accurately identifying true underlying covariate relationships on Vc/F.

Robustness of the final model

The model was fitted to 1000 bootstrap-replicated data sets to evaluate model stability and performance. Successful minimization was obtained for 875 runs, and bootstrap statistics were derived from all successful runs. Estimates of PK parameters from the final PopPK model were close to the respective median values from the bootstrap runs, and the 95% CIs had narrow widths, indicating that performance and stability of the final model were good. As part of sensitivity analyses, a power relationship of creatinine clearance on CL/F, replacing the power relationship of eGFR, was evaluated. This analysis resulted in a slight worsening of the OFV and was not retained. Next, a sensitivity analysis was performed to determine the impact of outliers excluded during model development. Model minimization was not successful, and the Vp/F and residual additive error estimates were inflated with increases of 31% and 159%, respectively. Finally, fixed allometric scaling on both CL/F and volume parameters was evaluated, but no improvement in the fit was observed with respect to the final model.

Evaluation of diagnostics for the final model

Goodness-of-fit plots for population-predicted (Figure 4a) and individual-predicted (Figure 4b) concentrations plotted against observed concentrations indicated adequate model fit. Although the population-predicted concentrations versus observed concentrations showed some overprediction at higher concentrations (>1000 ng/mL), this may have been due to a paucity of data at high doses (e.g., 150 mg). Scatterplots of CWRES versus population-predicted values (Figure 4c) and time since last dose stratified by RI category (Figure 4d) showed some bias observed in the higher concentration range or in higher RI categories; however, most data were well-predicted and there was no indication of systematic trends. The adequacy of introducing each covariate was assessed by comparing the random effect (ETA) versus covariate scatter plots from the base model and final model. For each covariate relationship identified in the model, there was a clear sign of improvement in the relative plot, as the trends in the ETA values initially visible for the base model disappeared in the final model. Visual predictive checks were stratified by phase I (Figure S3) and phase II and III (Figure S3) data using the final model; the final model predicted the observed median, 5th, and 95th percentiles of gefapixant concentrations with good accuracy. Evaluation of the final model using additional data from the extension periods of phase III studies was performed, and the resulting parameters were similar to those obtained in the primary analysis data set (data not shown).

Simulations

Exposures in target population after chronic administration of gefapixant 45 mg b.i.d.

Median geometric means across simulations for PK parameters of interest, including $AUC_{ss,0-12}$ and C_{max}, are summarized in Table S6. The geometric mean of the accumulation ratio of gefapixant upon multiple dosing was 1.65 (95% CI, 1.61–1.70).

Magnitude of covariate effects on the RCC/UCC and RI populations

In the phase II and III RCC and UCC populations, the magnitude of covariate effects on $AUC_{ss,0-12}$ for body

TABLE 1 Parameter estimates of the final PopPK model of gefapixant.

PK parameter	Estimate (95% CI)[a]	RSE, %	Shrinkage, %
Absorption rate constant (K_a), h^{-1}	2.25 (1.86, 2.85)	9.9	–
Apparent clearance (CL/F), L/h	10.3 (10.1, 10.5)	1.1	–
Apparent central volume of distribution (Vc/F), L	101 (96.9, 104)	1.8	–
Apparent intercompartmental clearance (Q/F), L/h	3.51 (2.7, 4.42)	12.8	–
Apparent peripheral volume (Vp/F), L	32.8 (26.9, 46.6)	12.7	–
Absorption lag time (ALAG), h	0.432 (0.415, 0.445)	1.7	–
eGFR power relationship on clearance (Cl_{eft})[b]	0.375 (0.317, 0.429)	8.4	–
Food effect on absorption rate for the F02 formulation (Ka_{EEDN})[b]	−0.594 (−0.675, −0.496)	7.7	–
Age power relationship on central volume (Vc_{AGE})[b]	0.0911 (0.0239, 0.162)	37.1	–
Sex relationship on central volume (Vc_{SEX})[b]	0.181 (0.138, 0.234)	13.6	–
Weight power relationship on central volume (Vc_{BW})[b]	0.541 (0.452, 0.627)	8.4	–
Age power relationship on clearance (CL_{AGE})[b]	−0.229 (−0.284, −0.171)	13.3	–
Weight power relationship on clearance (CL_{BW})[b]	0.35 (0.27, 0.43)	11.3	–
Sex relationship on clearance (CL_{SEX})[b]	0.0931 (0.0545, 0.133)	22.7	–
Interindividual variability on absorption rate (ω^2_{Ka})[c]	0.551 (0.379, 0.738)[d]	18.7	6.5
Interindividual variability on apparent clearance (ω^2_{CL})[c]	0.0708 (0.0612, 0.0808)[d]	6.7	15.4
Covariance between CL/F and Vc/F (ρ^2_{CL-Vc})	0.0176 (0.0106, 0.0276)	22.9	–
Interindividual variability on apparent central volume (ω^2_{Vc})[c]	0.0161 (0.0061, 0.0337)[d]	41.8	52.2
Proportional residual error (σ_{PROP})	0.303 (0.29, 0.316)	2.3	7.2
Additive residual error (σ_{ADD}), ng/mL	3.04 (2.3, 3.81)	15.4	7.2

Abbreviations: BW, body weight; CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; PK, pharmacokinetic; PopPK, population PK; RSE, relative standard error.

[a]CIs taken from bootstrap analysis.

[b]Continuous covariates centered around the following data median values: eGFR = 87.2 mL/min/1.73 m^2; BW = 74 kg; and age = 59 years. Categorical covariate references: sex = female; fed = fasted.

[c]K_a interindividual variability is informed by only phase I data, whereas CL/F and Vc/F interindividual variability are informed by all data.

[d]Percentage of CV calculated as sqrt((exp(ω^2) − 1)) × 100. Percentage of CV: ω^2_{Ka} = 85.7%; ω^2_{CL} = 27.1%; and ω^2_{Vc} = 12.7%.

weight, age, sex, and diagnosis of chronic cough was small (<20%; Figure 5a). However, RI had a larger impact on gefapixant exposure. For participants with mild, moderate, and severe RI (not requiring dialysis), the increase in AUC was predicted to be 1.17-, 1.46-, and 1.89-fold higher relative to participants with normal renal function. As the increase in predicted exposures in the severe RI category relative to participants with normal renal function was considered clinically relevant, additional dosage regimens were simulated for the severe RI population. Simulation results demonstrated that participants with severe RI receiving gefapixant 45 mg q.d. had exposures similar to those of participants with normal renal function receiving gefapixant 45 mg b.i.d. (Figure 5b). The dosage change from twice daily to once daily in patients with severe RI is further justified by half-life values of gefapixant: in typical patients with severe RI, gefapixant half-life is 15.1 h, compared with 8.4, 9.5, and 11.5 h in typical patients with normal renal function, mild RI, or moderate RI, respectively. Patients with severe RI receiving gefapixant 45 mg q.d. will not have the second peak associated with twice-daily dosing but will have the same total daily exposure as patients with normal renal function receiving gefapixant 45 mg b.i.d.

The effects of intrinsic factors on C_{max} at steady-state for the total phase II/III study population and populations stratified by RI categories were similar to the effects on $AUC_{ss,0-12}$ (Figure S4).

DISCUSSION

This paper describes the development of a PopPK model for gefapixant across phase I through III studies in healthy participants and participants with RCC or UCC. The phase II and III studies in the RCC and UCC population had sparse PK data; however, PK samples were collected at up to eight visits in the phase III studies, and time of sampling was random relative to the time from previous

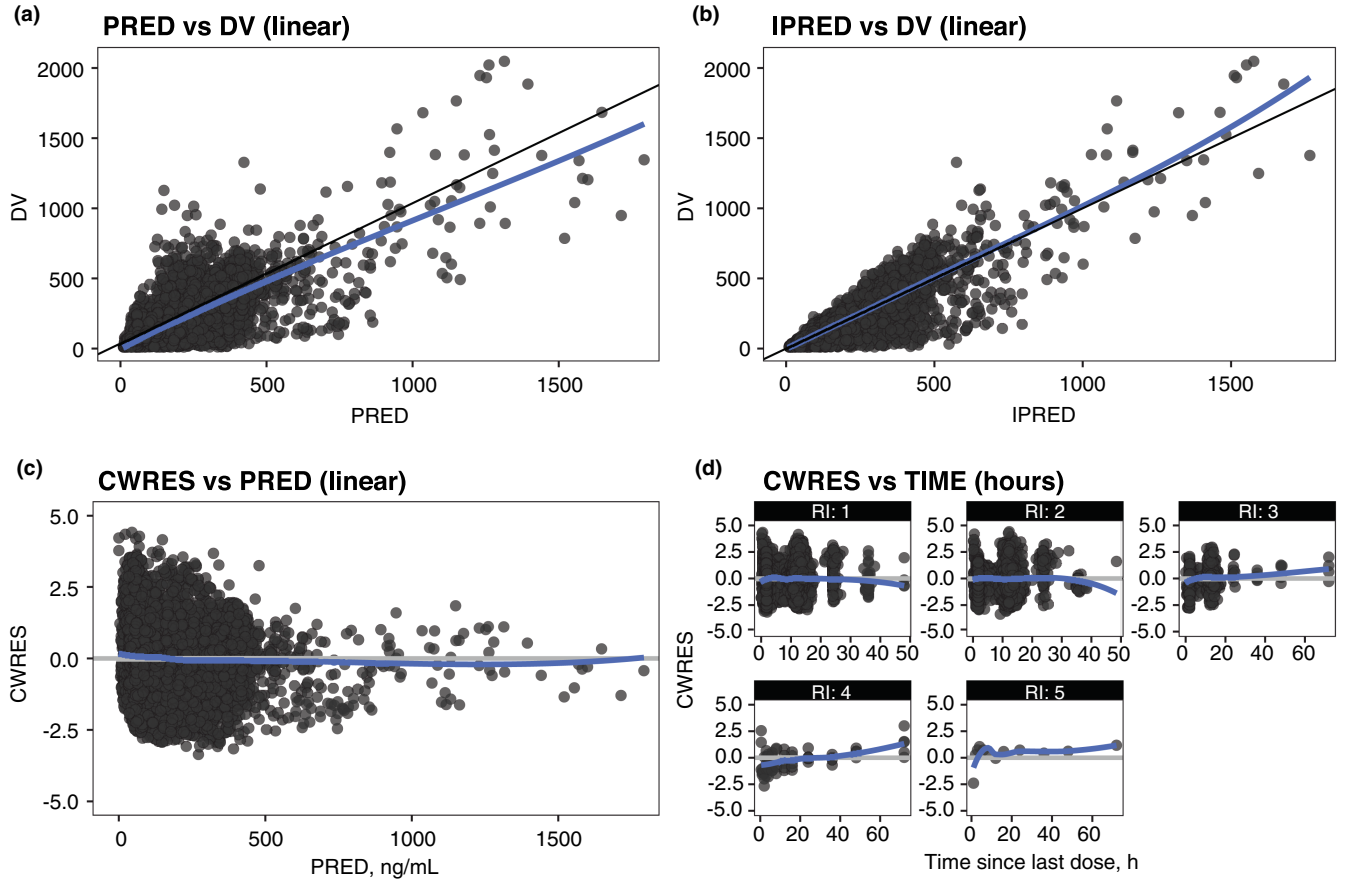

FIGURE 4 Goodness-of-fit plots for the final model. Scatterplots of (a) population-predicted concentrations and (b) individual-predicted concentrations against the observed concentration. Scatterplots of CWRES versus (c) population-predicted concentrations and (d) time since last dose, stratified by category of RI. For RI, 1 through 5 indicates normal, mild, moderate, severe, and very severe, respectively. CWRES, conditional weighted residual; DV, dependent variable; IPRED, individual-predicted concentration; PRED, population-predicted concentration; RI, renal impairment.

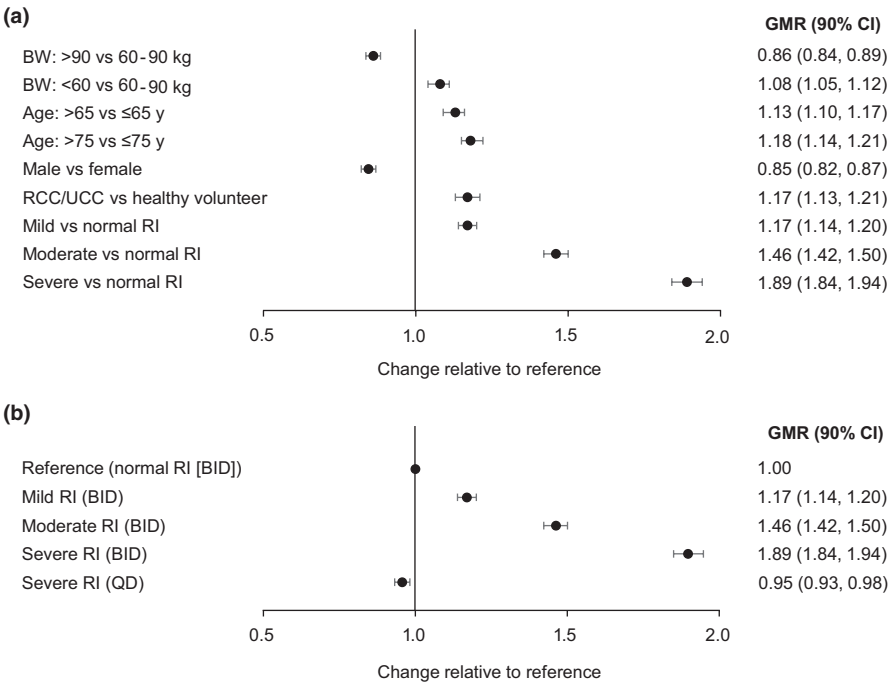

FIGURE 5 Impact of intrinsic factors on $AUC_{ss,0-12}$ of gefapixant (a) in the phase II/III study population after administration of gefapixant 45 mg b.i.d. and (b) in the RI population after administration of gefapixant 45 mg b.i.d. or 45 mg q.d. (reference: normal RI with gefapixant 45 mg b.i.d.). $AUC_{ss,0-12}$, area under the concentration curve versus time at steady-state; BW, body weight; GMR, geometric mean ratio; RCC, refractory chronic cough; RI, renal impairment; UCC, unexplained chronic cough.

dose, allowing proper characterization of the PK profile in the target population.

In this analysis, most parameters were estimated with good precision (RSEs for all parameters excluding age and IIV on Vc/F, <25%). Random-effect shrinkage for the final model was acceptable for the IIV on CL/F parameter (shrinkage 15%) but high for the IIV on Vc/F parameter (shrinkage 52%). This is consistent with our assumption that sparse PK data in phase II and III studies can estimate clearance well but has limitations in estimating volume (Vc/F) parameters.

Results suggest that gefapixant is a low- to moderate-variability drug. There was no difference in exposure between healthy participants and those with RCC or UCC after accounting for demographic factors. Although the effects of age, body weight, and sex on exposure were statistically significant, the magnitude of these effects was small (<20%; Figure 5a). Additionally, although race was identified as a statistically significant covariate during covariate model building, this was driven by the difference in CL/F in the "multiple" race category relative to other categories. The "multiple" race category comprised a small (~5%) proportion of the target population, suggesting the effect of race is not clinically relevant.

Consistent with gefapixant being primarily eliminated via renal excretion, eGFR was a statistically and clinically significant factor impacting gefapixant exposure (Figure 5). Compared with participants with normal renal function, those with RI had 1.17-fold (mild RI) to 1.89-fold (severe RI not requiring dialysis) higher exposure. The magnitude of these effects is numerically lower but directionally consistent with previous findings from a dedicated RI study ($n=6$ each for participants with normal renal function, moderate RI, severe RI, and ESRD).[26] The dedicated RI study predicted a 1.87-, 2.79-, and 3.76-fold higher exposure (AUC) for participants with mild, moderate, and severe RI, respectively, relative to matched controls.

The key difference between gefapixant exposures in the dedicated RI study and the current analysis is due to lower exposure in the reference populations with normal renal function, which led to the difference in fold change in RI populations (Figure 6). Multiple factors may have contributed to the lower exposure in participants with normal renal function in the dedicated RI study versus those in this analysis, including overall interstudy variability, smaller sample size, and higher mean eGFR (122 mL/min/1.73 m^2 vs. 104 mL/min/1.73 m^2) in the dedicated RI study. Although fold changes relative to normal renal function were different, the exposures in the dedicated RI study and current PopPK analysis are consistent in each RI category.

Considering a larger data set consisting of the target RCC and UCC population ($n=1555$ with 664, 817, and 74 participants in the normal renal function, mild RI, and moderate RI categories, respectively), this analysis provides a realistic prediction of the effects of RI on exposure in the intended patient population. Therefore, results from the PopPK model rather than the dedicated RI study

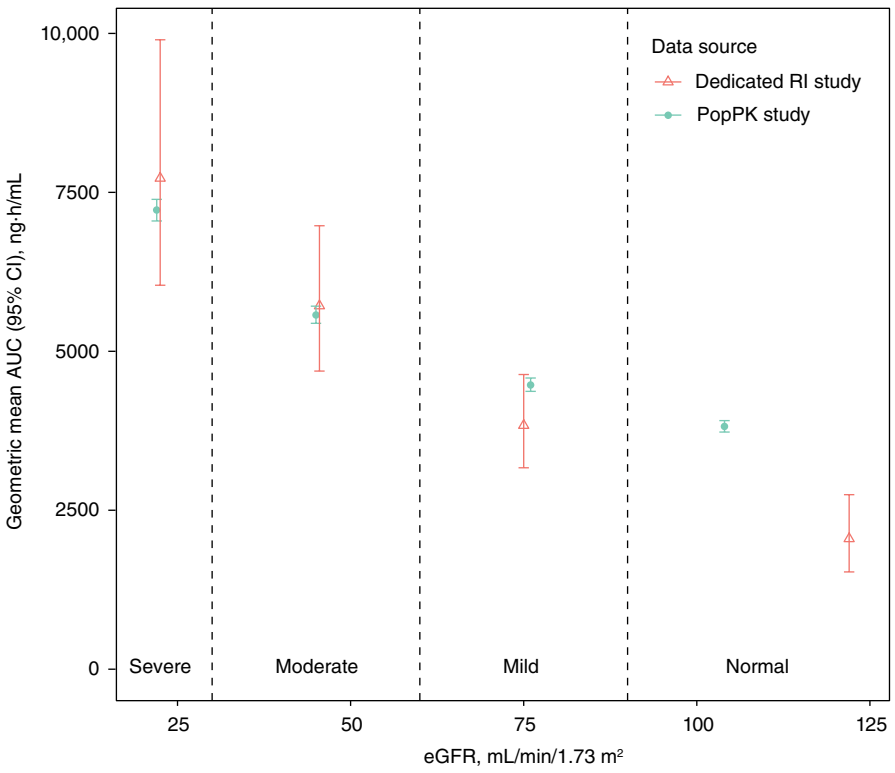

FIGURE 6 Gefapixant exposure in dedicated RI study and PopPK analysis. Projected AUC (and 95% CIs) for dedicated RI study (normalized to 45-mg multiple dosing) and PopPK analysis (simulated results based on modeling) at each category of renal function. AUC, area under the curve; CI, confidence interval; eGFR, estimated glomerular filtration rate; PK, pharmacokinetic; PopPK, population PK; RI, renal impairment.

were used to inform gefapixant dosage recommendations for patients with RI.

A limitation in the current analysis is that individuals on hemodialysis were not included. The impact of RI on gefapixant exposure for non-hemodialysis participants was estimated using the relationship between eGFR and CL/F, but the relationship between eGFR and CL/F for patients on hemodialysis is not clear and, hence, exposure in patients on hemodialysis cannot be predicted on the basis of eGFR.

The formulations evaluated in this analysis were F02 (an earlier formulation) and F04 (which includes both the prototype formulation F04 and phase III formulation F04A). Phase I relative bioavailability (formulation, PPI use, and food effect) studies concluded that fed status and concomitant use of a PPI impacted gefapixant exposures for F02 but not for F04. Therefore, in this PopPK analysis, food and PPI effects were assessed on F02 only. Food effect was found to be a statistically significant factor affecting K_a; however, PPI effect was not significant. The final market formulation F04B is compositionally similar to F04A, with the exception that F04B does not have citric acid as a formulation ingredient. Additionally, F04B has been shown to be bioequivalent to F04A in terms of gefapixant exposure.[25] Thus, findings from this PopPK analysis are expected to hold for the proposed commercial formulation.

CONCLUSIONS

Gefapixant is a low- to moderate-variability drug with most intrinsic (e.g., age, sex, and weight) and extrinsic (e.g., food effect) factors having no clinically relevant effects on exposure. The current analysis suggests that patients with severe RI are expected to have meaningfully higher gefapixant exposures compared with patients with normal renal function. Simulation results demonstrate that patients with mild or moderate RI do not require dosage adjustments; however, for patients with severe RI who are not on dialysis, once-daily (instead of twice-daily) dosing is recommended.

AUTHOR CONTRIBUTIONS

A.C., A.L., H.K., H.K.A., C.L., and F.G. wrote the manuscript. A.C., A.L., A.H., J.N., and F.G. designed the research. A.C., A.L., A.H., H.K.A., J.N., and F.G. performed the research. A.C., A.L., H.K., S.A.-O., J.A., H.K.A., J.N., and F.G. analyzed the data. A.C. contributed new reagents/analytical tools.

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CONFLICT OF INTEREST STATEMENT

A.C., A.H., S.A.-O., J.A., H.A., J.N., C.L., and F.G. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. A.L. and H.K. served as paid consultants for Merck & Co., Inc., Rahway, NJ, USA.

DATA AVAILABILITY STATEMENT

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to dataaccess@merck.com.

REFERENCES

1. Irwin RS, French CL, Chang AB, Altman KW. For the CHEST expert cough panel. Classification of cough as a symptom in adults and management algorithms: CHEST guideline and expert panel report. *Chest*. 2018;153:196-209.
2. Chamberlain SA, Garrod R, Douiri A, et al. The impact of chronic cough: a cross-sectional European survey. *Lung*. 2015;193:401-408.
3. Çolak Y, Nordestgaard BG, Laursen LC, Afzal S, Lange P, Dahl M. Risk factors for chronic cough among 14,669 individuals from the general population. *Chest*. 2017;152:563-573.
4. Satia I, Mayhew AJ, Sohel N, et al. Prevalence, incidence and characteristics of chronic cough among adults from the Canadian longitudinal study on aging. *ERJ Open Res*. 2021;7:00160-2021.
5. Everett CF, Kastelik JA, Thompson RH, Morice AH. Chronic persistent cough in the community: a questionnaire survey. *Cough*. 2007;3:1-7.
6. Zeiger RS, Schatz M, Hong B, et al. Patient-reported burden of chronic cough in a managed care organization. *J Allergy Clin Immunol Pract*. 2021;9:1624-1637.
7. Richards D, Gever JR, Ford AP, Fountain SJ. Action of MK-7264 (gefapixant) at human P2X3 and P2X2/3 receptors and in vivo efficacy in models of sensitisation. *Br J Pharmacol*. 2019;176:2279-2291.
8. Kyorin Pharmaceutical Co. Ltd. MSD K.K. receives manufacturing and marketing approval of LYFNUA® Tablets, world's first selective P2X3 receptor antagonist for the treatment of chronic cough. https://www.kyorin-pharm.co.jp/en/news/2022/001603.shtml. Accessed March 28, 2023
9. Lyfnua®, Filmtabletten (Gefapixantum). Swissmedic. https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/new-medicines/lyfnua-filmtabletten-gefapixantum.html. Accessed March 28, 2023
10. Ford AP. In pursuit of P2X3 antagonists: novel therapeutics for chronic pain and afferent sensitization. *Purinergic Signal*. 2012;8(Suppl 1):3-26.

11. Mansoor SE, Lü W, Oosterheert W, Shekhar M, Tajkhorshid E, Gouaux E. X-ray structures define human P2X(3) receptor gating cycle and antagonist action. *Nature*. 2016;538:66-71.
12. Ford A, Undem B. The therapeutic promise of ATP antagonism at P2X3 receptors in respiratory and urological disorders. *Front Cell Neurosci*. 2013;7:267.
13. Smith JA, Badri H. Cough: new pharmacology. *J Allergy Clin Immunol Pract*. 2019;7:1731-1738.
14. Basoglu OK, Barnes PJ, Kharitonov SA, Pelleg A. Effects of aerosolized adenosine 5′-triphosphate in smokers and patients with COPD. *Chest*. 2015;148:430-435.
15. Basoglu OK, Pelleg A, Essilfie-Quaye S, Brindicci C, Barnes PJ, Kharitonov SA. Effects of aerosolized adenosine 5′-triphosphate vs adenosine 5′-monophosphate on dyspnea and airway caliber in healthy nonsmokers and patients with asthma. *Chest*. 2005;128:1905-1909.
16. Dosch M, Gerber J, Jebbawi F, Beldi G. Mechanisms of ATP release by inflammatory cells. *Int J Mol Sci*. 2018;19:1222.
17. McGovern AE, Short KR, Moe AAK, Mazzone SB. Translational review: neuroimmune mechanisms in cough and emerging therapeutic targets. *J Allergy Clin Immunol*. 2018;142:1392-1402.
18. Birring S, Morice A, Smith J, et al. Responder analyses for patient-reported outcomes in a pooled analysis of two phase III randomized placebo controlled trials of gefapixant, a P2X3 receptor antagonist for the treatment of chronic cough. Poster presented at: Annual International Conference of the American Thoracic Society; May 14-19, 2021; Virtual.
19. McGarvey LP, Birring SS, Morice AH, et al. Efficacy and safety of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet*. 2022;399:909-923.
20. Abdulqawi R, Dockry R, Holt K, et al. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet*. 2015;385:1198-1205.
21. Smith JA, Kitt MM, Morice AH, et al. Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. *Lancet Respir Med*. 2020;8:775-785.
22. McCrea JB, Hussain A, Ma B, et al. Assessment of pharmacokinetic interaction between gefapixant (MK-7264), a P2X3 receptor antagonist, and the OATP1B1 drug transporter substrate pitavastatin. *Clin Pharmacol Drug Dev*. 2022;11:406-412.
23. Nussbaum JC, Hussain A, Ma B, et al. Characterization of the absorption, metabolism, excretion, and mass balance of gefapixant in humans. *Pharmacol Res Perspect*. 2022;10:e00924.
24. Muccino DR, Morice AH, Birring SS, et al. Design and rationale of two phase 3 randomised controlled trials (COUGH-1 and COUGH-2) of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough. *ERJ Open Res*. 2020;6:00284-2020.
25. Gupta P, Hussain A, Ford AP, et al. Clinical formulation bridging of gefapixant, a P2X3-receptor antagonist, for the treatment of chronic cough. *Clin Pharmacol Drug Dev*. 2022;11:1054-1067.
26. Nussbaum JC, Hussain A, Min KC, et al. Effects of renal impairment on the pharmacokinetics of gefapixant, a P2X3 receptor antagonist. *J Clin Pharmacol*. 2022;62:1435-1444.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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